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Recent Advances in Combined Antiviral Therapies and Emerging Antiviral Strategies: A Comprehensive Review.

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ABSTRACT

This review article explores the wide range of currently available antiviral treatment options and newly developed strategies to combat viral illnesses. The authors emphasize that viruses are infectious agents that rely on host cells for reproduction and dissemination, and that the complex structures and transmission methods of different viruses must be taken into account when developing treatment plans. The article also highlights the significant global health and economic costs associated with viral infections, including the high mortality rates of many viral illnesses. The authors provide detailed descriptions of key antiviral drug classes and their mechanisms of action, including direct-acting antivirals, interferons, and ribavirin analogs. In addition to these established therapies, the review highlights newly developed strategies for treating viral illnesses that aim to target the host immune system or disrupt viral replication more effectively. These include the use of fusion inhibitors, CRISPR/Cas9 gene editing technology, and small interfering RNA molecules, among others. Overall, this review provides a comprehensive guide to the current options for treating viral infections, and will be of value to healthcare professionals and researchers working in the field of infectious disease.

Keywords: viruses; antiviral drugs; antiviral strategies; antiviral therapy; combined antiviral treatment

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INTRODUCTION

A virus is an infectious agent that requires a host cell to reproduce and carry out its life cycle and dissemination. The genome of a virus is made up of DNA or RNA surrounded by a capsid composed of proteins. Although some viruses contain a lipid envelope around the protein capsid. After entering the host cell, the viral genome manipulates the host cell machinery for protein synthesis, genomic replication, and virus assembly. The new virions released upon lysis of the host cell can interact with other cells and cause further infection. Viruses have varying structures, genetic materials, and modes of transmission, all of which are crucial in understanding how they cause disease and devising therapies for their treatment [1,2].

Emerging viral illnesses most often caused by mutated strains of existing viruses, and re-emergence of previously existing viruses have led to enormous health and economic burdens on human life [3]. Infectious diseases are responsible for 20% of global mortality, additionally viral illnesses have given rise to 70% of these deaths [4,5]. During 20th century, there have been epidemics in which many people have died because of some diseases caused by viruses; for example, estimated 50 million people have died due to the H1N1 influenza strain in 1918 worldwide [3]. 35 Million people have died because of acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus (HIV) since 1981 [6,7]. Severe acute respiratory syndrome (SARS) emerged in 2003 has caused 8098 infections and 774 of these were reported to have died in the World [8]. After that, Middle East respiratory syndrome (MERS) emerged first in 2012 in Saudi Arabia and has a mortality rate of 35%, approximately [9]. Ebola infections were first appeared in 1976 and the average Ebola case fatality rate is around 50% [10]. Zika virus (ZKV) infections was first identified in Uganda in 1947. Between 1960 and 1980, sporadic human infections were defined across Africa and Asia but, since 2007 epidemics of ZKV disease have been recorded in Africa, the Americas, and the Pacific. This infection is associated with Guillain-Barré syndrome, neuropathy and myelitis in adults and children. Additionally, a causal link between ZKV and congenital malformations was confirmed in 2016 [11]. Lastly, the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started in December 2019 and reached 768 million confirmed cases of COVID-19 with 6,953 million deaths worldwide as of 31 July 2023 [12]. Therefore, the discovery of antiviral drugs against viral diseases that seriously threatens human health has always been a field of interest for researchers. The development of antiviral drugs begun in the 1960's and the approval of iodine as the first antiviral drug in June 1963 was a groundbreaking event in antiviral drug research [13,14]. Between 1963 and 2016, we had an arsenal of more than 90 antiviral drugs including over 20 anti-Hepatitis C virus drugs and 40 anti-HIV drugs [13]. In the last 30 years, significant improvements have been succeeded, especially in the development of antiretroviral and against hepatit C virus (HCV) drugs [15]. Most available antiviral drugs specifically target viral enzymes and they have some important advantages such as a clear target, high specifity levels, and strong activity as well as some disadvantages such as a limited antiviral spectrum and drug resistance [16]. Now, the use of combinations of antiviral drugs and vaccines is the most common strategy for the prevention and treatment of human viral infections [4,17]. Nevertheless, the increase in drug-resistant virus strains is a serious problem [18]. Additionally, current vaccines are useless against mutated or novel viruses [19].

Vaccines are a substantial and effective tool against viral infections. However, the vaccine development is a long way which can be got hard by viral genome mutations [20].

Drug repurposing provides available or previously approved drugs as new drugs for new clinical indications. Drug repurposing processes can be worked rapidly owing to approved drug compound libraries [21]. These drugs have some advantages so that they can be applied directly to clinical trials or potentially used as emergency treatment [20].

The use of two or more drugs together for the treatment of a disease is known as 'combination therapy'. Drug combinations can cause adverse effects due to drug-drug interactions. On the other hand, cautious use has some advantages. This therapy can simplify targeting multiple pathways to support drug synergy. Thus, useful effects arise. Synergistic drug combinations result in lower individual drug doses. Eventually, patient tolerability rises and drug toxicities decrease [22]. Combination therapy also has the advantage of suppressing or delaying the onset of drug resistance, which is frequently observed in many diseases. Combination therapy has become the standard-of-care treatment for chronic viral diseases caused by HIV and HCV, anymore. This therapy mode does not always cure the disease. However, it can

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significantly improve quality of life and prolong life by increasing therapeutic efficacy and preventing drug resistance. Experience to data from treatments for severe and chronic viral disease reveals that combination therapies including two to three medications would be beneficial in the treatment of emerging infectious diseases such as COVID-19 [20].

In this paper, we consider available antiviral drugs, highlighting strategies and targets for antiviral drug discovery as well as drug combination therapy for current and emerging viral diseases.

Antiviral Drugs

Antiviral drugs are agents used against diseases caused by viruses. Now, we have an arsenal of 179 antiviral drugs. Currently, 4.4% of 4051 approved drugs are antiviral agents but, 10 of 88 have been withdrawn by virtue of side effects [23,24]. Antiviral drugs consist of small molecules, peptides, neutralizing antibodies, interferons (IFNs), Crispr-Cas systems, si/shRNAs, and other nucleic acid polymers (NAPs) [25–30]. Of these, IFNs are host-directed biologics; neutralizing antibodies, peptides, NAPs, and Crispr/Cas are used as virus-directed interventions, primarily. On the other hand, small molecule antiviral agents can be either virus- or host-directed drugs. Antiviral drugs can target the virus and the host. Virus-targeting antiviral agents target viral proteins, viral nucleic acids or lipid envelopes. Oseltamivir (Figure 1), which is a viral neuraminidase inhibitor and used in influenza, can be given as an example of antiviral drugs that target the virus. Antiviral drugs targeting the host are used cellular factors that mediate virus replication. Maraviroc (Figure 1) is a host-targeting drug that targets the cellular CCR5 receptor used in the treatment of AIDS [31].

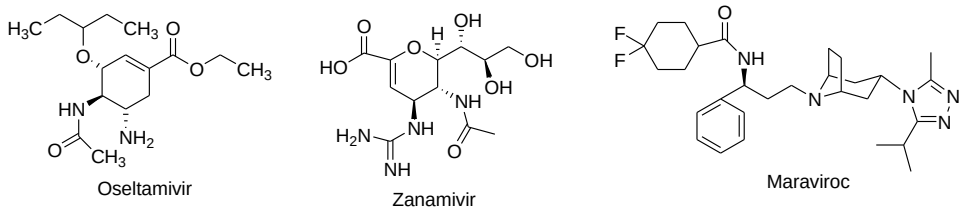


Figure 1: The chemical formulas of neuraminidase inhibitors, oseltamivir and zanamivir, and CCR5 antagonist maraviroc accentuated in the text.

Antiviral Strategies and Targets

The traditional approach of random screening and the subsequent optimization of lead compounds *via* systematic chemical synthesis are both resource-wasting and time-consuming [32], so it would be beneficial to develop different strategies. Some strategies have been developed to find novel antiviral compounds with new scaffolds and better resistance profile, recently (Figure 2). Application of these newly developed medicinal chemistry strategies are expected to help to discover potent antiviral agents against current and future viral pandemics [33]. Some new research strategies which have been developed recently, are listed as follows:

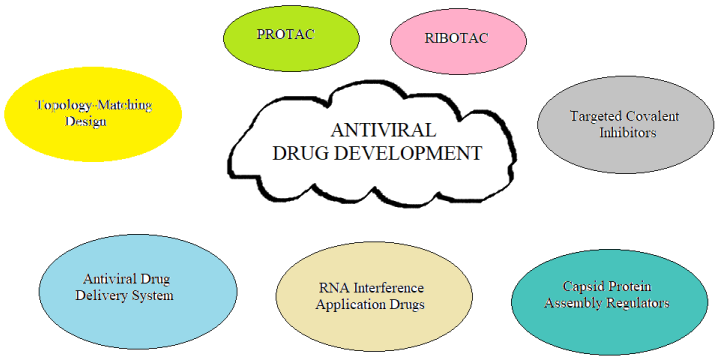


Figure 2: Recent strategies in antiviral drug discovery.

Proteolysis Targeting Chimera (PROTAC)

Targeting PROTAC compounds used the ubiquitin-proteasome system can target degradation of proteins by promoting and achieving of target proteins [34,35]. PROTACs are hetero-bifunctional molecules containing 3 components: a ligand for the related protein, an E3 ubiquitin ligase recruitment ligand and a linker. These molecules are tied to the related protein with one end and the other end of PROTACs is tied to an E3 ligase for targeting to shorten the distance between them *in vivo.* In the second step, the E3 ligase provides the transfer of ubiquitin to the related protein, at last the ubiquitylated protein is destroyed by the proteasome [36–38]. PROTAC technology has been used by Yang *et al.* to develop anti-HCV compounds thus, these researchers aimed to induce viral proteasome degradation [39]. The PROTAC molecule linked to the ligand of CRL4CRBN has the ability to induce HCV NS3/4A protease degradation that contributes to its antiviral activity [40]. Moreover, PROTAC molecules are compounds with low toxicity and high selectivity and it can be used in low doses [41].

Ribonuclease Targeting Chimera (RIBOTAC)

RIBOTAC which is a new strategy aims to degrade RNA. This technology transforms RNA-binding molecules into RNA-degrading molecules to break down the viral genome. For this, a small molecule connects to RNA and activates ribonuclease L (RNase L) [42]. Haniff and co-workers synthesized a series of small molecules targeting a functional structure inside of the RNA genome of SARS-CoV-2. It was found that compounds C5 can stabilize the frameshift element and has inhibitory activity on the frameshift ability of the SARS-CoV-2 frameshift element, considerably. Simultaneously, compounds 39 structure was changed using RIBOTAC technology and attached to a small molecule that can recruit RNase L to succeed the degradation of SARS-CoV-2 mRNA [43].

Targeted Covalent Inhibitors

The rational design of targeted covalent inhibitors has largely been realized by improvements in structural biology and bioinformatics. These inhibitors can form covalent bonds with specific target proteins thus, charges in the conformation of proteins occur; ultimately interferes with the normal function of the protein [44]. Covalent binding with the target can occur in two ways: the inhibitor can bind to the target reversibly or the ligand reacts to create a covalent bond with the functional groups in the protein structure [45,46]. Targeted covalent inhibitors have gained popularity due to their selectivity, and efficacy properties in the antiviral field, recently [19].

Emerging resistance associated with the Tyr181Cys (Y181C) mutation in HIV-1 reverse transcriptase enzyme (RT) is one of the biggest problems in the development of nonnucleoside RT inhibitors (NNRTIs). Covalent inhibitors of Y181C RT that could entirely eliminate activity of the resistant mutant were discovered. In this study, derivatives carrying groups capable of forming covalent bonds with the sulfhydryl group of Cys181 such as chloromethylamide and acrylamide have led to the positive results. This is the first successful application of the irreversible covalent inhibition strategy to HIV-1 RT [47].

Topology-Matching Design

Influenza a virus uses hemagglutinin and neuraminidase to interact between host cells and virion [48]. The virion of influenza A virus, an enveloped RNA virus, is a nanosized particle of about 100 nm, topologically [48,49]. It is important to match the size and topology of the virion and nanoinhibitor to ensure competitive binding with virus/cell interaction using nanoinhibitors [19]. Nie and co-workers designed a nano-inhibitor with a nano-topological structure matching the influenza A virus virion by using of “topology-matching design” strategy and succeeded some inhibitory effects on hemagglutinin and neuraminidase [50,51].

Antiviral Drug Delivery System

Human serum albumin, whose primary function is to act as a transporter of various molecules, is the most abundant protein in sera [52]. Small molecular drugs bound to human serum albumin by non-covalent bond are resistant to enzymatic degradation and renal clearance thus, these drugs have slower clearance and extended their half-life *in vivo* [53]. The discovery of albuvirtide, an HIV fusion in-

hibitor, has shown us that targeting human serum albumun is a suitable strategy for the development of long-acting antiviral drugs [19].

Cholesterol is an abundant substance in the cell membranes of the human body. Modified nucleic acids and peptides can pass lipid bilayers *via* cholesterol conjugation and uptake by cells [54]. Targeting the membrane can be especially reasonable strategy for improving of the antiviral efficacy of neuraminidase inhibitors (Figure 1) [55]. It has been found that the conjugate of zanamivir (Figure 1), an antiviral agent with cholesterol, extended the neuraminidase inhibitor effect of the drug and causes strong activity against drug-resistant influenza viruses [56].

RNA Interference Application Drugs

RNA interference means stopping expression of the specific gene provided by double-stranded RNA [57]. Some RNA interference application drugs such as ARB-1467 (Phase II clinical trial), RG-6004 (Phase I clinical trial), GSK-3389404, and GSK-3228836 (Phase II clinical trial) are currently being developed for the treatment of chronic hepatitis B [58–60].

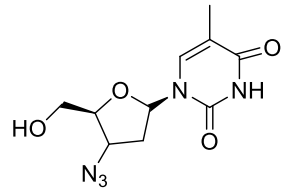
3Capsid Protein Assembly Regulators

Hepatitis B virus (HBV) capsid protein assembly regulator can prevent the replication of HBV virus by devastating the function of the capsid [61]. The HBV capsid can preserve the viral genome encapsulated in the capsid, and also it supports the reverse transcription of pgRNA to create DNA [62,63]. Heteroaryldihydropyrimidines which can increase the hydrophobic interaction between adjacent core protein dimers are HBV capsid assembly modulators and speed up the degradation of capsid proteins [64,65]. HBV capsid protein assembly regulators are BAY 41-4109 (first generation), GIS-4 (second generation, phase I clinical trial), and HAP-R10 (third generation, phase I clinical trial) [66,67].

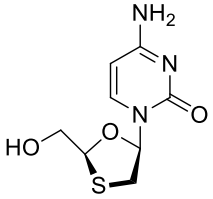
Drug Combination Therapy

HIV

When left untreated, chronic HIV infections lead to AIDS and the immune system is compromised [68]. Even now, there is no definitive treatment or vaccine approved for AIDS. Effective suppression of HIV loads a significant reduction in AIDS and HIV-related mortality have been achieved *via* therapeutic improvements. Azidothymidine (AZT, Zidovudine; Figure 3), the first antiretroviral-a nucleoside reverse transcriptase inhibitor (NRTI), reduced rates of mortality in AIDS patients [69]. Nevertheless, monotherapy lost effectiveness with the emergence of drug resistance, quickly. Because viral genome mutations and lack of proofreading often occurs in RNA viruses, HIV mutation rates were high [70]. With the introduction of protease inhibitors (PI) in therapy, the standard treatment for HIV has changed, drastically. Combination antiretroviral therapy (cART) consisting of two NRTIs and a PI has been accepted as standard treatment for HIV infections and considerable decreases in HIV infection progression to AIDS and mortality rates have been achieved with the application of this therapy mode [70–72]. Combination of two drugs (for example, Dovato and Juluca [Table 1]) can be used in the initial treatment of HIV infections, too [73]. Considering clinical parameters and contraindications, it is now possible to choose drug combinations from different US Food and Drug Administration (FDA)-approved antiviral drugs with different mechanism of action. Single pills including drug combinations result in improved clinical outcomes because patient compliance and treatment adherence rates increased [74,75]. Consequently, HIV has turned into a manageable disease with cART applications [76].



Azidothymidine (AZT, Zidovudine)



Lamivudine

Figure 3: Representative examples of NRTIs. Lamivudine is combined with dolutegravir in Dovato.

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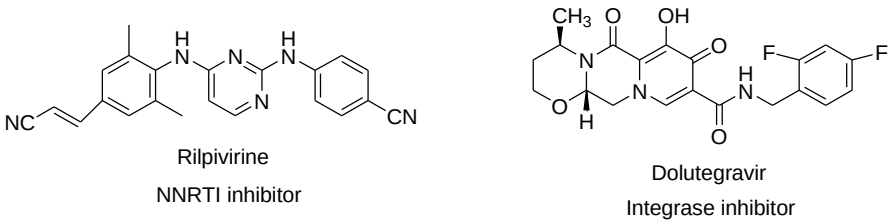

Figure 4: Chemical structures of antiviral drugs in combination in Juluca.

Table 1: Approved and tested antiviral drug combinations.

Drug names	Disease
Dolutegravir, lamivudine (Dovato)	HIV
Dolutegravir, rilpivirine (Juluca)	HIV
IFN, RBV	HCV
IFN, RBV, Telaprevir/Boceprevir	HCV
IFN, RBV, Sofosbuvir/Daclatasvir	HCV
Sofosbuvir, Velpatasvir	HCV
Glecaprevir, Pibrentasvir	HCV
Favipiravir, Oseltamivir	Influenza
MEDI8852, Oseltamivir	Influenza
Nirmatrelvir, Ritonavir (Paxlovid)	COVID-19

Lenacapavir (Sunlenca, Figure 5) is a first-class capsid inhibitor that was approved by the FDA and European Commission in the second half of 2022 to treat adults with multi-drug resistant HIV infection [77–79]. Lenacapavir inhibits HIV-1 in picomolar level *in vitro.* The drug, which can be given orally or subcutaneously, shows little or no cross-resistance with existing antiretroviral agents. It has extended pharmacokinetics when administered subcutaneously [80–83]. Lenacapavir, by combined with other antiretroviral(s), is used in heavily treatment-experienced adult patients who experiencing a failure of their current therapy because of resistance, intolerance or safety considerations [79,84]. Lenacapavir inhibits HIV-1 virus by interfering with a number of essential steps of the viral lifecycle [79].

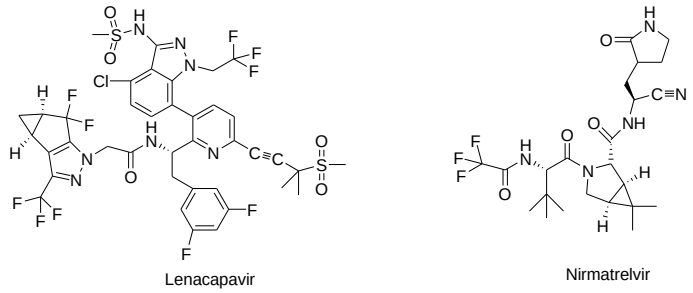

Figure 5: The chemical structures of newest antiviral agents emphasized in this review.

HCV

It may be possible to treat HCV infections with antiviral agents because HCV viral genome replicates in the cytoplasm without the need for integration into the host cell [85]. Acute HCV infections can be eliminated by the immune system. This condition is predicted to occur in ~ 20-30% of infected adults. Chronic HCV develops in the remaining 70-80% of infected individuals. In the following years, these people have a higher risk of developing cirrhosis, liver cancer, and other liver diseases [86]. HCV is associated with chronic inflammation thus, it rises the risk of developing vascular diseases, insulin resistance/diabetes, and extrahepatic cancers [85].

We currently do not have an effective vaccine against HCV. Antiviral agents made possible a cure rate of >95% of HCV infections thus, the risk of death due to HCV-related complications reduced, considerably [87].

For the last 20 years, non-PEGylated and later PEGylated IFN have been used in the treatment of HCV. The PI ribavirin (RBV, Figure 6) has sometimes been added to this treatment [85]. The cure rate for the treatment with IFN/RBV (Table 1) did not exceed 50% according as HCV genotypes and other comorbidities. At the same time, this therapy mode has led to adverse reactions. In 2011, with the approval of NS3/4A PIs such as telaprevir (Figure 6) or boceprevir (Figure 6), triple-combination therapy was started which rose the cure rates to 75% (Table 1) [88]. Cure rates rose drastically to 95% with the use of newer direct-acting antiviral agents such as sofosbuvir, a HCV NS5B inhibitor (Figure 6), and daclatasvir, a NS5A inhibitor (Figure 6). Also, no increase in significant adverse effects was noted [85]. Treatment for HCV using direct-acting antiviral agents is tailored to age, HCV genotype, stage of liver disease, or other underlying conditions. For the simplified initial treatment of drug-naïve HCV, two different combinations can be recommended: a combination of sofosbuvir + velpatasvir (Figure 6) for 12 weeks or glecaprevir (Figure 6) + pibrentasvir (Figure 6) for 8 weeks (Table 1) [89]. In a recent clinical trial conducted in drug-naïve HCV patients, it was determined that the use of two different three-drug combinations reduced the treatment period from 12 to 6 weeks [90]. Hence, combination therapy for HCV resulted in good efficacy, minimal adverse effects, and the shortening of the treatment duration. Combination therapy is also beneficial for drug resistance and HCV infections with other comorbidities. New drug combinations have shown high success rates in HCV patients who have received direct-acting antivirals and whose disease has relapsed [91–94]. Combination of drugs for HIV/HCV co-infections were tested in clinical trials. HIV suppression and high sustained virological response for HCV provided without major adverse effects [95].

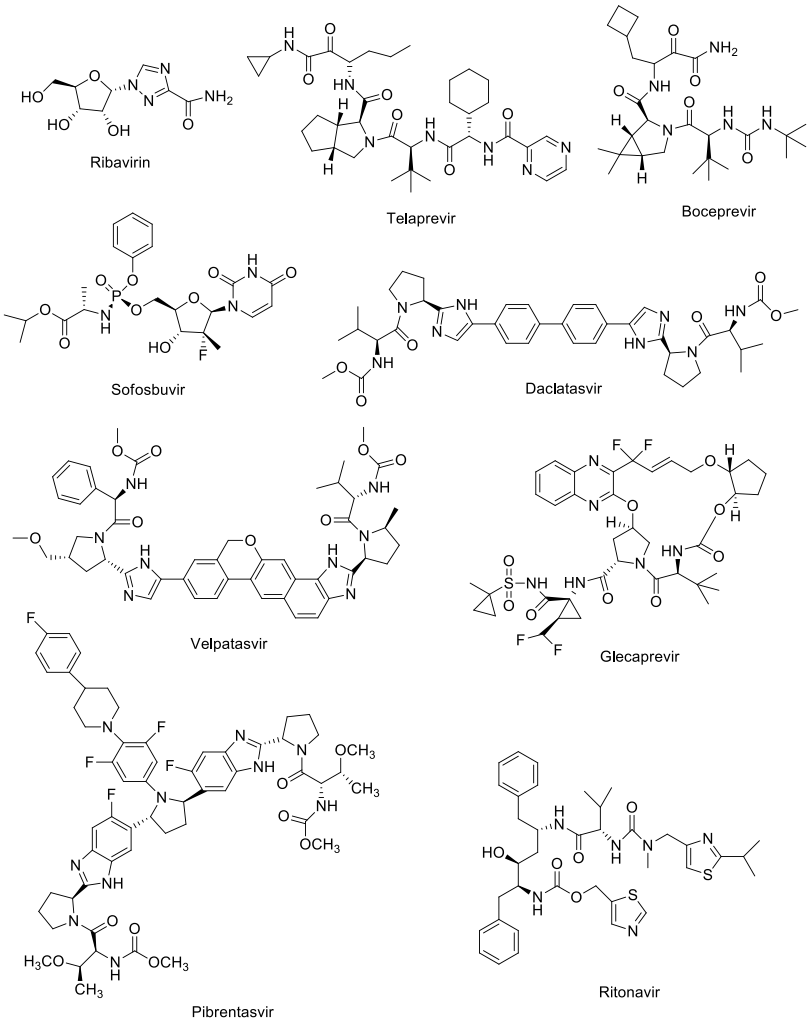

Figure 6: The chemical structures of PI class of antiviral drugs.

Influenza

Influenza infections are still common at ~ 1 billion cases worldwide and 650000 people die annually due to influenza [96]. There are vaccines against influenza, presently. However, these vaccines need to be modified and administered every year due to often viral mutations. The effectiveness of influenza vaccines has changed from 19% to 60% [97]. Influenza viruses have rapid mutation properties, which facilitates drug resistance and necessitates changes in treatment. For influenza infections, there are several antiviral drugs available. Between 1980 and 2000, antiviral resistance developed against the adamantane-derived drugs rimantadine and amantadine (Figure 7) [98]. It was known that most influenza strains are still susceptible to many neuraminidase inhibitors (Figure 1) [96,99], but most of the virus strains developed resistance to the neuraminidase inhibitor oseltamivir (Figure 1) [99]. Drug combinations can be used to overcome this problem [100]. In a recent study, the combination of favipiravir (Figure 7) + oseltamivir (Figure 1) was tested against severe influenza in a small cohort of patients (Table 1) [101]. It was observed that combination therapy might accelerate recovery compared with monotherapy with oseltamivir (Figure 1), alone. Several monoclonal antibodies were tested in Phase II trial and it was found that they were safe and could reduce duration of disease in cases of uncomplicated influenza[102–105]. A combination of monoclonal antibody MEDI8852 + oseltamivir (Figure 1) did not indicate recovery in clinical outcomes compared with monotherapy with each individual agent in uncomplicated influenza (Table 1) [103]. On the other hand, this combination has been found to be useful against severe disease or future resistant influenza strains. Another monoclonal antibody VIS410 is currently being tested as monotherapy or combination in patients with influenza A [106].

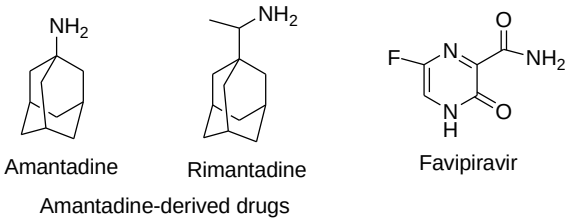

Figure 7: The chemical formulas of amantadine-derived drugs mentioned in this paper and favipiravir.

Drug Combination Therapy for Emerging Viral Diseases

Rapid development of antiviral agents is imperative for the treatment of new and emerging infectious diseases. Whereas it takes a long time for new drugs to FDA approval. The discovery of vaccines and drug combinations containing specific antiviral agents against viral disease caused by HIV, HCV, influenza, and emergent coronavirus COVID-19 is required. The most important advantage of combination therapy is to increase the therapeutic efficacy by targeting host cell pathways as well as multiple viral targets. Thus, it may be possible to reduce drug resistance [20]. Synergistic drug combinations make it possible to effectively treat diseases with lower doses in the absence of adverse effects. Drug combinations can be tested directly in the clinic and *in vitro* screening results can identify effective combinations. For this, suitable methods are available [107].

Another technique commonly used to identify drug combinations with synergistic activity is matrix drug combination studies [22,108]. Different reference models are used. Moreover, synergistic and additive combinations can be specified. Each model introduces unique assumptions and obtained results can changed with different models used and with input parameters [109].

Current Treatment Options for Emerging Viral Diseases

Ebola virus (EBOV), MERS, and ZIKV infections are currently endemic in some parts of the world and have not turned into a pandemic. Although some potential treatment options for MERS [110], ZIKV [111], and EBOV [112] have been identified *via* drug-repurposing studies, there are currently no drugs approved for these illnesses. Clinical trials for EBOV treatment are conducted with single drugs rather than combination of drugs. In late 2020, an Ebola glycoprotein-directed monoclonal antibody was approved by the FDA for EBOV therapy. Because these antibody treatments are administered intravenously

and more effective in reducing mortality rates in patients who are not severely ill [113]. WHO recommends strongly for the use of two monoclonal antibody treatments in the treatment of Ebola: mAb114 (Ansuvimab; Ebanga) and REGN-EB3 (Inmazeb) [10]. Though, developing new agents for EBOV therapy is urgently needed.

After the emergence of COVID-19 in late 2019, three COVID-19 vaccines with the inclusion of two RNA vaccines (Moderna's mRNA-1273 and Pfizer's BNT162b2) [114–116], and the single-dose Janssen vaccine, have been granted Emergency Use Authorization (EUA) by the FDA and other regulatory agencies. These vaccines have played an important role in providing much-needed relief from the COVID-19 pandemic. However, it is unclear how long the vaccines will provide protection against the virus. In some countries of the world such as the UK, South Africa, and Brazil SARS-CoV-2 variants with mutations in the spike protein have already been observed [117].

Nirmatrelvir, a SARS-CoV-2 main protease inhibitor (Figure 5) and ritonavir, a HIV-1 protease inhibitor (Figure 6), and CYP3A inhibitor combination was fully approved by the FDA on May 25, 2023 to treat mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19 [84,118,119]. A recent combination for the treatment of COVID-19 (Paxlovid) is the nirmatrelvir + ritonavir combination (Table 1).

Drug repurposing and repositioning studies have been carried out intensively against COVID-19. At the time of writing (August 2023), there were 4136 registered clinical trials on ClinicalTrials.gov based on a search of 'COVID-19' with 'drug' and 2676 publications for the search term of 'drug repurposing for COVID-19' in PubMed. Remdesivir is the small molecule drug approved by the FDA and other regulatory agencies for hospitalized COVID-19 patients. Despite all these studies on COVID-19, the success of the vaccines and drugs obtained is limited so there is urgency to develop efficient therapy options against this virus.

CONCLUSIONS

Chronic viral infections caused by HIV and hepatitis B, besides the emergence of new viruses (e. g. EBV, and coronaviruses) demonstrated the need for more innovative strategies for the development of more potent antiviral agents. In this review, we have defined some recent emerging strategies used for developing antiviral agents to improve drug resistance and potency. Of these strategies, PROTAC, RIBOTAC, targeted covalent inhibitors, topology-matching design, antiviral drug delivery system, RNA interference application drugs, and capsid protein assembly regulators were discussed above. Nevertheless, there are some limitations about them. When PROTACs are high molecular weight molecules, they can not cross cell membranes to induce intracellular protein degradation, and limited water solubility arises resulting the low bioavailability. Likewise, the large molecular weights of RIBOTACs and multivalent binding molecules also create problem. Additionally, covalent inhibitors have potential toxic properties and some side effects [19].

DNA-encoded chemistry technology [120], genome editing technology [121], nucleic acid aptamer technology [122], and ligand discovery based on protein self-assembly [123] are also the techniques for the development of new and potent antiviral agents. For this purpose, natural products obtained from plants grown in different parts of the world provide an unlimited resource, as well [124,125]. Uncovering mechanisms such as RNA capping machinery [126], the ubiquitous hydrophobic protein structure (viroporins [127], and host protein involved in viral infection [128] which are found in different viruses and are likely to be targets for the discovery of new antiviral agents, will also help the development of them. The use of medicinal chemistry together with bioinformatics and artificial intelligence technology, high-throughput phenotypic screening and reverse pharmacophore matching virtual screening is useful to search for new drug indications [19].

Although the treatment of chronic viral diseases such as HIV and HBV has been improved with the introduction of some newly developed antiviral drugs, a complete cure of these viral diseases has not been achieved. These diseases, which require long-term drug therapy for their treatments, may cause epidemics and there is still a possibility of recurrence. Unfortunately, drug resistance remains the biggest problem in antiviral therapy [129,130]. Now, we have not any effective medications for the treatment of SARS, MERS, ZIKV, EBOV, and COVID-19. SARS-CoV-2 emerged in the city of Wuhan in China in December 2019 and called as COVID-19 later caused a pandemic that killed millions of people worldwide. The need

for new antiviral drugs with different mechanisms of action has been more understood with the COVID-19 outbreak. Unfortunately, we also know that we are not prepared for a new viral pandemic. When we encounter a new viral pandemic, drug repositioning, prodrug strategy, and natural products seem to be effective strategies. We hope that the ongoing studies will successfully enable the discovery of new strategies, and the development of new agents as well as new drug combinations for the treatment of viral diseases, and thus, cure viral diseases and epidemics in the future.

REFERENCES

[1] S. Peng, H. Wang, Z. Wang, Q. Wang, Progression of Antiviral Agents Targeting Viral Polymerases, Molecules. 27 (2022). https://doi.org/10.3390/molecules27217370.

[2] M.G. Mateu, Introduction: The Structural Basis of Virus Function, in: 2013: pp. 3–51. https://doi.org/10.1007/978-94-007-6552-8_1.

[3] [1918 Pandemic. Centers for Disease Control and Prevention Website., www.cdc.gov/flu/pandemic-resources/1918-pandemic-h1n1.html. Updated March 20 2019 [Accessed May 14, 2021], (2021).

[4] E. De Clercq, Fifty Years in Search of Selective Antiviral Drugs, Journal of Medicinal Chemistry. 62 (2019) 7322–7339. https://doi.org/10.1021/acs.jmedchem.9b00175.

[5] E. De Clercq, Antivirals and antiviral strategies, Nature Reviews Microbiology. 2 (2004) 704–720. https://doi.org/10.1038/nrmicro975.

[6] L. Lu, S. Su, H. Yang, S. Jiang, Antivirals with common targets against highly pathogenic viruses, Cell. 184 (2021) 1604–1620. https://doi.org/10.1016/j.cell.2021.02.013.

[7] L.B. Cohn, N. Chomont, S.G. Deeks, The Biology of the HIV-1 Latent Reservoir and Implications for Cure Strategies, Cell Host & Microbe. 27 (2020) 519–530. https://doi.org/10.1016/j.chom.2020.03.014.

[8] Severe Acute Respiratory Syndrome. Centers for Disease Control and Prevention Website., www.cdc.gov/sars/about/fs-sars.html/. [Accessed August 1, 2023]., (2023).

[9] Middle East Respiratory Syndrome Virus., WHO Website. www.who.int/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov) Updated August 5, 2022. [Accessed August 1, 2023]., (2023).

[10] Ebola Virus Disease. WHO Website., https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease Updated April 20,

[11] Z.V. Disease., WHO Website. https://www.who.int/news-room/fact-sheets/detail/zika-virus Updated December 8, 2022. [Accessed August 1, 2023]., (2023).

[12] WHO Coronavirus (COVID-19) Dashboard., https://covid19.who.int [Accessed August 8, 2023]., (2023).

[13] I. Capua, D.J. Alexander, Human Health Implications of Avian Influenza Viruses and Paramyxoviruses, European Journal of Clinical Microbiology & Infectious Diseases. 23 (2004) 1–6. https://doi.org/10.1007/s10096-003-1059-3.

[14] D.D. Richman, N. Nathanson, Antiviral Therapy, in: Viral Pathogenesis, Elsevier, 2016: pp. 271–287. https://doi.org/10.1016/B978-0-12-800964-2.00020-3.

[15] G. Bertino, Chronic hepatitis C: This and the new era of treatment, World Journal of Hepatology. 8 (2016) 92. https://doi.org/10.4254/wjh.v8.i2.92.

[16] R. Vardanyan, V. Hruby, Antiviral Drugs. In Synthesis of Best-Seller Drugs; Academic Press: Cambridge, MA, USA, (2016).

[17] P. Zhan, C. Pannecouque, E. De Clercq, X. Liu, Anti-HIV Drug Discovery and Development: Current Innovations and Future Trends, Journal of Medicinal Chemistry. 59 (2016) 2849–2878. https://doi.org/10.1021/acs.jmedchem.5b00497.

[18] Y. Ma, E. Frutos-Beltrán, D. Kang, C. Pannecouque, E. De Clercq, L. Menéndez-Arias, X. Liu, P. Zhan, Medicinal chemistry strategies for discovering antivirals effective against drug-resistant viruses, Chemical Society Reviews. 50 (2021) 4514–4540. https://doi.org/10.1039/D0CS01084G.

[19] S. Xu, D. Ding, X. Zhang, L. Sun, D. Kang, B. Huang, X. Liu, P. Zhan, Newly Emerging Strategies in Antiviral Drug Discovery: Dedicated to Prof. Dr. Erik De Clercq on Occasion of His 80th Anniversary, Molecules. 27 (2022) 850. https://doi.org/10.3390/molecules27030850.

[20] Z.A. Shyr, Y.-S. Cheng, D.C. Lo, W. Zheng, Drug combination therapy for emerging viral diseases, Drug Discovery Today. 26 (2021) 2367–2376. https://doi.org/10.1016/j.drudis.2021.05.008.

[21] C. Skuta, M. Popr, T. Muller, J. Jindrich, M. Kahle, D. Sedlak, D. Svozil, P. Bartunek, Probes & Drugs portal: an interactive, open data resource for chemical biology, Nature Methods. 14 (2017) 759–760. https://doi.org/10.1038/nmeth.4365.

[22] T. Bobrowski, L. Chen, R.T. Eastman, Z. Itkin, P. Shinn, C.Z. Chen, H. Guo, W. Zheng, S. Michael, A. Simeonov, M.D. Hall, A. V. Zakharov, E.N. Muratov, Synergistic and Antagonistic Drug Combinations against SARS-CoV-2, Molecular Therapy. 29 (2021) 873–885. https://doi.org/10.1016/j.ymthe.2020.12.016.

[23] S. Chaudhuri, J.A. Symons, J. Deval, Innovation and trends in the development and approval of antiviral medicines: 1987–2017 and beyond, Antiviral Research. 155 (2018) 76–88. https://doi.org/10.1016/j.antiviral.2018.05.005.

[24] D.S. Wishart, Y.D. Feunang, A.C. Guo, E.J. Lo, A. Marcu, J.R. Grant, T. Sajed, D. Johnson, C. Li, Z. Sayeeda, N. Assempour, I. Iynkkaran, Y. Liu, A. Maciejewski, N. Gale, A. Wilson, L. Chin, R. Cummings, D. Le, A. Pon, C. Knox, M. Wilson, DrugBank 5.0: a major update to the DrugBank database for 2018, Nucleic Acids Research. 46 (2018) D1074–D1082. https://doi.org/10.1093/nar/gkx1037.

[25] P.I. Andersen, A. Ianevski, H. Lysvand, A. Vitkauskiene, V. Oksenych, M. Bjørås, K. Telling, I. Lutsar, U. Dumpis, Y. Irie, T. Tenson, A. Kantele, D.E. Kainov, Discovery and development of safe-in-man broad-spectrum antiviral agents, International Journal of Infectious Diseases. 93 (2020) 268–276. https://doi.org/10.1016/j.ijid.2020.02.018.

[26] H. de Buhr, R.J. Lebbink, Harnessing CRISPR to combat human viral infections, Current Opinion in Immunology. 54 (2018) 123–129. https://doi.org/10.1016/j.coi.2018.06.002.

[27] A. Levanova, M.M. Poranen, RNA Interference as a Prospective Tool for the Control of Human Viral Infections, Frontiers in Microbiology. 9 (2018). https://doi.org/10.3389/fmicb.2018.02151.

[28] F. Lin, H.A. Young, Interferons: Success in anti-viral immunotherapy, Cytokine & Growth Factor Reviews. 25 (2014) 369–376. https://doi.org/10.1016/j.cytogfr.2014.07.015.

[29] G. Salazar, N. Zhang, T.-M. Fu, Z. An, Antibody therapies for the prevention and treatment of viral infections, Npj Vaccines. 2 (2017) 19. https://doi.org/10.1038/s41541-017-0019-3.

[30] A. Vaillant, Nucleic acid polymers: Broad spectrum antiviral activity, antiviral mechanisms and optimization for the treatment of hepatitis B and hepatitis D infection, Antiviral Research. 133

(2016) 32–40. https://doi.org/10.1016/j.antiviral.2016.07.004.

[31] A. Ianevski, R. Yao, R.M. Simonsen, V. Myhre, E. Ravlo, G.D. Kaynova, E. Zusinaite, J.M. White, S.J. Polyak, V. Oksenych, M.P. Windisch, Q. Pan, E. Lastauskienė, A. Vitkauskienė, A. Matukevičius, T. Tenson, M. Bjørås, D.E. Kainov, Mono- and combinational drug therapies for global viral pandemic preparedness, IScience. 25 (2022) 104112. https://doi.org/10.1016/j.isci.2022.104112.

[32] G. Wu, T. Zhao, D. Kang, J. Zhang, Y. Song, V. Namasivayam, J. Kongsted, C. Pannecouque, E. De Clercq, V. Poongavanam, X. Liu, P. Zhan, Overview of Recent Strategic Advances in Medicinal Chemistry, Journal of Medicinal Chemistry. 62 (2019) 9375–9414. https://doi.org/10.1021/acs.jmedchem.9b00359.

[33] Q. Xu, F. Jiang, G. Guo, E. Wang, M.R. Younis, Z. Zhang, F. Zhang, Z. Huan, C. Fan, C. Yang, H. Shen, J. Chang, Targeted hot ion therapy of infected wound by glycol chitosan and polydopamine grafted Cu-SiO2 nanoparticles, Nano Today. 41 (2021) 101330. https://doi.org/10.1016/J.NANTOD.2021.101330.

[34] A.C. Lai, C.M. Crews, Induced protein degradation: an emerging drug discovery paradigm, Nature Reviews Drug Discovery. 16 (2017) 101–114. https://doi.org/10.1038/nrd.2016.211.

[35] M. Pettersson, C.M. Crews, PROteolysis TArgeting Chimeras (PROTACs) — Past, present and future, Drug Discovery Today: Technologies. 31 (2019) 15–27. https://doi.org/10.1016/j.ddtec.2019.01.002.

[36] S.-L. Paiva, C.M. Crews, Targeted protein degradation: elements of PROTAC design, Current Opinion in Chemical Biology. 50 (2019) 111–119. https://doi.org/10.1016/j.cbpa.2019.02.022.

[37] X. Li, Y. Song, Proteolysis-targeting chimera (PROTAC) for targeted protein degradation and cancer therapy, Journal of Hematology & Oncology. 13 (2020) 50. https://doi.org/10.1186/s13045-020-00885-3.

[38] B.E. Smith, S.L. Wang, S. Jaime-Figueroa, A. Harbin, J. Wang, B.D. Hamman, C.M. Crews, Differential PROTAC substrate specificity dictated by orientation of recruited E3 ligase, Nature Communications. 10 (2019) 131. https://doi.org/10.1038/s41467-018-08027-7.

[39] Z. Yang, Y. Sun, Z. Ni, C. Yang, Y. Tong, Y. Liu, H. Li, Y. Rao, Merging PROTAC and molecular glue for degrading BTK and GSPT1 proteins concurrently, Cell Research. 31 (2021) 1315–1318. https://doi.org/10.1038/s41422-021-00533-6.

[40] M. Békés, D.R. Langley, C.M. Crews, PROTAC targeted protein degraders: the past is prologue, Nature Reviews Drug Discovery. 21 (2022) 181–200. https://doi.org/10.1038/s41573-021-00371-6.

[41] W. Xu, B. Sun, F. Wu, M. Mohammadniaei, Q. Song, X. Han, W. Wang, M. Zhang, N. Zhou, J. Shen, Manganese single-atom catalysts for catalytic-photothermal synergistic anti-infected therapy, Chemical Engineering Journal. 438 (2022) 135636. https://doi.org/10.1016/J.CEJ.2022.135636.

[42] H. Li, J. Dong, M. Cai, Z. Xu, X.-D. Cheng, J.-J. Qin, Protein degradation technology: a strategic paradigm shift in drug discovery, Journal of Hematology & Oncology. 14 (2021) 138. https://doi.org/10.1186/s13045-021-01146-7.

[43] M.G. Costales, J.L. Childs-Disney, H.S. Haniff, M.D. Disney, How We Think about Targeting RNA with Small Molecules, Journal of Medicinal Chemistry. 63 (2020) 8880–8900.

https://doi.org/10.1021/acs.jmedchem.9b01927.

[44] R.A. Bauer, Covalent inhibitors in drug discovery: from accidental discoveries to avoided liabilities and designed therapies, Drug Discovery Today. 20 (2015) 1061–1073. https://doi.org/10.1016/j.drudis.2015.05.005.

[45] M. Gehringer, S.A. Laufer, Emerging and Re-Emerging Warheads for Targeted Covalent Inhibitors: Applications in Medicinal Chemistry and Chemical Biology, Journal of Medicinal Chemistry. 62 (2019) 5673–5724. https://doi.org/10.1021/acs.jmedchem.8b01153.

[46] R. Lonsdale, R.A. Ward, Structure-based design of targeted covalent inhibitors, Chemical Society Reviews. 47 (2018) 3816–3830. https://doi.org/10.1039/C7CS00220C.

[47] A.H. Chan, W.-G. Lee, K.A. Spasov, J.A. Cisneros, S.N. Kudalkar, Z.O. Petrova, A.B. Buckingham, K.S. Anderson, W.L. Jorgensen, Covalent inhibitors for eradication of drug-resistant HIV-1 reverse transcriptase: From design to protein crystallography, Proceedings of the National Academy of Sciences. 114 (2017) 9725–9730. https://doi.org/10.1073/pnas.1711463114.

[48] L.J. Calder, P.B. Rosenthal, Cryomicroscopy provides structural snapshots of influenza virus membrane fusion, Nature Structural & Molecular Biology. 23 (2016) 853–858. https://doi.org/10.1038/nsmb.3271.

[49] R.E. Amaro, P.U. Ieong, G. Huber, A. Dommer, A.C. Steven, R.M. Bush, J.D. Durrant, L.W. Votapka, A Computational Assay that Explores the Hemagglutinin/Neuraminidase Functional Balance Reveals the Neuraminidase Secondary Site as a Novel Anti-Influenza Target, ACS Central Science. 4 (2018) 1570–1577. https://doi.org/10.1021/acscentsci.8b00666.

[50] C. Nie, B. Parshad, S. Bhatia, C. Cheng, M. Stadtmüller, A. Oehrl, Y. Kerkhoff, T. Wolff, R. Haag, Topology-Matching Design of an Influenza-Neutralizing Spiky Nanoparticle-Based Inhibitor with a Dual Mode of Action, Angewandte Chemie International Edition. 59 (2020) 15532–15536. https://doi.org/10.1002/anie.202004832.

[51] C. Nie, M. Stadtmüller, H. Yang, Y. Xia, T. Wolff, C. Cheng, R. Haag, Spiky Nanostructures with Geometry-matching Topography for Virus Inhibition, Nano Letters. 20 (2020) 5367–5375. https://doi.org/10.1021/acs.nanolett.0c01723.

[52] M.J. Matos, Learning from nature: the role of albumin in drug delivery, Future Medicinal Chemistry. 10 (2018) 983–985. https://doi.org/10.4155/fmc-2018-0053.

[53] Z. Liu, X. Chen, Simple bioconjugate chemistry serves great clinical advances: albumin as a versatile platform for diagnosis and precision therapy, Chemical Society Reviews. 45 (2016) 1432–1456. https://doi.org/10.1039/C5CS00158G.

[54] B. Su, C. Yao, Q.-X. Zhao, W.-P. Cai, M. Wang, H.-Z. Lu, Y.-Y. Chen, L. Liu, H. Wang, Y. He, Y.-H. Zheng, L.-H. Li, J.-F. Chen, J.-H. Yu, B. Zhu, M. Zhao, Y.-T. Sun, W.-H. Lun, W. Xia, L.-J. Sun, L.-L. Dai, T.-Y. Jiang, M.-X. Wang, Q.-S. Zheng, H.-Y. Peng, Y. Wang, R.-J. Lu, J.-H. Hu, H. Xing, Y.-M. Shao, D. Xie, T. Zhang, F.-J. Zhang, H. Wu, Efficacy and safety of the long-acting fusion inhibitor albuvirtide in antiretroviral-experienced adults with human immunodeficiency virus-1: interim analysis of the randomized, controlled, phase 3, non-inferiority TALENT study, Chinese Medical Journal. 133 (2020) 2919–2927. https://doi.org/10.1097/CM9.0000000000001273.

[55] M. von Itzstein, The war against influenza: discovery and development of sialidase inhibitors, Nature Reviews Drug Discovery. 6 (2007) 967–974. https://doi.org/10.1038/nrd2400.

[56] X. Lv, P. Wang, C. Li, S. Cheng, Y. Bi, X. Li, Zanamivir–Cholesterol Conjugate: A Long-Acting

Neuraminidase Inhibitor with Potent Efficacy against Drug-Resistant Influenza Viruses, Journal of Medicinal Chemistry. 64 (2021) 17403–17412. https://doi.org/10.1021/acs.jmedchem.1c01531.

[57] K. Nganvongpanit, H. Müller, F. Rings, M. Gilles, D. Jennen, M. Hölker, E. Tholen, K. Schellander, D. Tesfaye, Targeted suppression of E-cadherin gene expression in bovine preimplantation embryo by RNA interference technology using double-stranded RNA, Molecular Reproduction and Development. 73 (2006) 153–163. https://doi.org/10.1002/mrd.20406.

[58] S. Agarwal, V. Pandey, Antioxidant Enzyme Responses to NaCl Stress in Cassia angustifolia, Biologia Plantarum. 48 (2004) 555–560. https://doi.org/10.1023/B:BIOP.0000047152.07878.e7.

[59] M.G. Martinez, F. Villeret, B. Testoni, F. Zoulim, Can we cure hepatitis B virus with novel direct-acting antivirals?, Liver International. 40 (2020) 27–34. https://doi.org/10.1111/liv.14364.

[60] A. Vaillant, HBsAg, Subviral Particles, and Their Clearance in Establishing a Functional Cure of Chronic Hepatitis B Virus Infection, ACS Infectious Diseases. 7 (2021) 1351–1368. https://doi.org/10.1021/acsinfecdis.0c00638.

[61] A. Diab, A. Foca, F. Zoulim, D. Durantel, O. Andrisani, The diverse functions of the hepatitis B core/capsid protein (HBc) in the viral life cycle: Implications for the development of HBc-targeting antivirals, Antiviral Research. 149 (2018) 211–220. https://doi.org/10.1016/j.antiviral.2017.11.015.

[62] M. Nassal, Hepatitis B viruses: Reverse transcription a different way, Virus Research. 134 (2008) 235–249. https://doi.org/10.1016/j.virusres.2007.12.024.

[63] Z. Tan, K. Pionek, N. Unchwaniwala, M.L. Maguire, D.D. Loeb, A. Zlotnick, The Interface between Hepatitis B Virus Capsid Proteins Affects Self-Assembly, Pregenomic RNA Packaging, and Reverse Transcription, Journal of Virology. 89 (2015) 3275–3284. https://doi.org/10.1128/JVI.03545-14.

[64] B. Venkatakrishnan, S.P. Katen, S. Francis, S. Chirapu, M.G. Finn, A. Zlotnick, Hepatitis B Virus Capsids Have Diverse Structural Responses to Small-Molecule Ligands Bound to the Heteroaryldihydropyrimidine Pocket, Journal of Virology. 90 (2016) 3994–4004. https://doi.org/10.1128/JVI.03058-15.

[65] L.-Y. Mak, D.K.-H. Wong, W.-K. Seto, C.-L. Lai, M.F. Yuen, Hepatitis B core protein as a therapeutic target, Expert Opinion on Therapeutic Targets. 21 (2017) 1153–1159. https://doi.org/10.1080/14728222.2017.1397134.

[66] S.J. Stray, A. Zlotnick, BAY 41-4109 has multiple effects on Hepatitis B virus capsid assembly, Journal of Molecular Recognition. 19 (2006) 542–548. https://doi.org/10.1002/jmr.801.

[67] L. Chen, J. Liang, An overview of functional nanoparticles as novel emerging antiviral therapeutic agents, Materials Science and Engineering: C. 112 (2020) 110924. https://doi.org/10.1016/j.msec.2020.110924.

[68] R.C. Gallo, L. Montagnier, The Discovery of HIV as the Cause of AIDS, New England Journal of Medicine. 349 (2003) 2283–2285. https://doi.org/10.1056/NEJMp038194.

[69] M.A. Fischl, D.D. Richman, M.H. Grieco, M.S. Gottlieb, P.A. Volberding, O.L. Laskin, J.M. Leedom, J.E. Groopman, D. Mildvan, R.T. Schooley, G.G. Jackson, D.T. Durack, D. King, The Efficacy of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex, New

England Journal of Medicine. 317 (1987) 185–191. https://doi.org/10.1056/NEJM198707233170401.

[70] B.S. Peters, K. Conway, Therapy for HIV, Advances in Dental Research. 23 (2011) 23–27. https://doi.org/10.1177/0022034511399082.

[71] M.O. Akanbi, K. Scarsi, B. Taiwo, R.L. Murphy, Combination Nucleoside/Nucleotide Reverse Transcriptase Inhibitors for Treatment of HIV Infection, Expert Opinion on Pharmacotherapy. 13 (2012) 65–79. https://doi.org/10.1517/14656566.2012.642865.

[72] T. Cihlar, M. Fordyce, Current status and prospects of HIV treatment, Current Opinion in Virology. 18 (2016) 50–56. https://doi.org/10.1016/j.coviro.2016.03.004.

[73] Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV Website., https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/what-start-initial-combination-regimens-antiretroviral-naive Updated September 21, 2022. [Accessed August 3, 2023]., (2023).

[74] S. Scott Sutton, J. Magagnoli, J.W. Hardin, Impact of Pill Burden on Adherence, Risk of Hospitalization, and Viral Suppression in Patients with HIV Infection and AIDS Receiving Antiretroviral Therapy, Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 36 (2016) 385–401. https://doi.org/10.1002/phar.1728.

[75] J. Cohen, A. Beaubrun, R. Bashyal, A. Huang, J. Li, O. Baser, Real-world adherence and persistence for newly-prescribed HIV treatment: single versus multiple tablet regimen comparison among US medicaid beneficiaries, AIDS Research and Therapy. 17 (2020) 12. https://doi.org/10.1186/s12981-020-00268-1.

[76] H. Samji, A. Cescon, R.S. Hogg, S.P. Modur, K.N. Althoff, K. Buchacz, A.N. Burchell, M. Cohen, K.A. Gebo, M.J. Gill, A. Justice, G. Kirk, M.B. Klein, P.T. Korthuis, J. Martin, S. Napravnik, S.B. Rourke, T.R. Sterling, M.J. Silverberg, S. Deeks, L.P. Jacobson, R.J. Bosch, M.M. Kitahata, J.J. Goedert, R. Moore, S.J. Gange, Closing the Gap: Increases in Life Expectancy among Treated HIV-Positive Individuals in the United States and Canada, PLoS ONE. 8 (2013) e81355. https://doi.org/10.1371/journal.pone.0081355.

[77] T.-Y.T.O. for P.L.W.M.-D.R.H. Gilead: Sunlenca® (lenacapavir) Receives FDA Approval as a First-in-Class, https://www.gilead.com/news-and-press/press-room/press-releases/2022/12/sunlenca-lenacapavir-receives-fda-approval-as-a-firstinclass-twiceyearly-treatment-option-for-people-living-with-multidrug-resistant-hiv [Accessed June 14, 2023]., (2023).

[78] the O.T.-Y.H.T.O. Gilead Press Releases: Gilead Announces First Global Regulatory Approval of Sunlenca® (Lenacapavir), https://www.gilead.com/news-and-press/press-room/press-releases/2022/8/gilead-announces-first-global-regulatory-approval-of-sunlenca-lenacapavir-the-only-twiceyearly-hiv-treatment-option [Accessed June 14, 2023]., (2023).

[79] EMA Approved Drug Products: Sunlenca (lenacapavir) Subcutaneous Injection or Oral Tablets., chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.ema.europa.eu/en/documents/product-information/sunlenca-epar-product-information_en.pdf [Accessed June 14, 2023]., (2023).

[80] S. Zhuang, B.E. Torbett, Interactions of HIV-1 Capsid with Host Factors and Their Implications

for Developing Novel Therapeutics, Viruses. 13 (2021) 417. https://doi.org/10.3390/v13030417.

[81] J.O. Link, M.S. Rhee, W.C. Tse, J. Zheng, J.R. Somoza, W. Rowe, R. Begley, A. Chiu, A. Mulato, D. Hansen, E. Singer, L.K. Tsai, R.A. Bam, C.-H. Chou, E. Canales, G. Brizgys, J.R. Zhang, J. Li, M. Graupe, P. Morganelli, Q. Liu, Q. Wu, R.L. Halcomb, R.D. Saito, S.D. Schroeder, S.E. Lazerwith, S. Bondy, D. Jin, M. Hung, N. Novikov, X. Liu, A.G. Villaseñor, C.E. Cannizzaro, E.Y. Hu, R.L. Anderson, T.C. Appleby, B. Lu, J. Mwangi, A. Liclican, A. Niedziela-Majka, G.A. Papalia, M.H. Wong, S.A. Leavitt, Y. Xu, D. Koditek, G.J. Stepan, H. Yu, N. Pagratis, S. Clancy, S. Ahmadyar, T.Z. Cai, S. Sellers, S.A. Wolckenhauer, J. Ling, C. Callebaut, N. Margot, R.R. Ram, Y.-P. Liu, R. Hyland, G.I. Sinclair, P.J. Ruane, G.E. Crofoot, C.K. McDonald, D.M. Brainard, L. Lad, S. Swaminathan, W.I. Sundquist, R. Sakowicz, A.E. Chester, W.E. Lee, E.S. Daar, S.R. Yant, T. Cihlar, Clinical targeting of HIV capsid protein with a long-acting small molecule, Nature. 584 (2020) 614–618. https://doi.org/10.1038/s41586-020-2443-1.

[82] S.M. Bester, G. Wei, H. Zhao, D. Adu-Ampratwum, N. Iqbal, V. V. Courouble, A.C. Francis, A.S. Annamalai, P.K. Singh, N. Shkriabai, P. Van Blerkom, J. Morrison, E.M. Poeschla, A.N. Engelman, G.B. Melikyan, P.R. Griffin, J.R. Fuchs, F.J. Asturias, M. Kvaratskhelia, Structural and mechanistic bases for a potent HIV-1 capsid inhibitor, Science. 370 (2020) 360–364. https://doi.org/10.1126/science.abb4808.

[83] N. Margot, R. Ram, M. Rhee, C. Callebaut, Absence of Lenacapavir (GS-6207) Phenotypic Resistance in HIV Gag Cleavage Site Mutants and in Isolates with Resistance to Existing Drug Classes, Antimicrobial Agents and Chemotherapy. 65 (2021). https://doi.org/10.1128/AAC.02057-20.

[84] FDA Approved Drug Products: PAXLOVID (nirmatrelvir and ritonavir) tablets, co-packaged for oral use. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217188s000lbl.pdf [Accessed June 14, 2023]., (2023).

[85] L. Parlati, C. Hollande, S. Pol, Treatment of hepatitis C virus infection, Clinics and Research in Hepatology and Gastroenterology. 45 (2021) 101578. https://doi.org/10.1016/j.clinre.2020.11.008.

[86] J.D. Stuart, E. Salinas, A. Grakoui, Immune system control of hepatitis C virus infection, Current Opinion in Virology. 46 (2021) 36–44. https://doi.org/10.1016/j.coviro.2020.10.002.

[87] Hepatitis C. WHO Website., www.who.int/news-room/fact-sheets/detail/hepatitis-c. Updated July 12, 2023. [Accessed August 3, 2023]., (2023).

[88] E. Pawlowska, J. Szczepanska, A. Koskela, K. Kaarniranta, J. Blasiak, Dietary Polyphenols in Age-Related Macular Degeneration: Protection against Oxidative Stress and Beyond, Oxidative Medicine and Cellular Longevity. 2019 (2019) 1–13. https://doi.org/10.1155/2019/9682318.

[89] HCV Guidance: Recommendations for Testing, Managing, AASLD/IDSA panel website. http://hcvguidelines.org Updated October 24, 2022. [Accessed August 3, 2023]., (2023).

[90] A. Kohli, A. Osinusi, Z. Sims, A. Nelson, E.G. Meissner, L.L. Barrett, D. Bon, M.M. Marti, R. Silk, C. Kotb, C. Gross, T.A. Jolley, S. Sidharthan, T. Petersen, K. Townsend, D. Egerson, R. Kapoor, E. Spurlin, M. Sneller, M. Proschan, E. Herrmann, R. Kwan, G. Teferi, R. Talwani, G. Diaz, D.E. Kleiner, B.J. Wood, J. Chavez, S. Abbott, W.T. Symonds, G.M. Subramanian, P.S. Pang, J.

McHutchison, M.A. Polis, A.S. Fauci, H. Masur, S. Kottilil, Virological response after 6 week triple-drug regimens for hepatitis C: a proof-of-concept phase 2A cohort study, The Lancet. 385 (2015) 1107–1113. https://doi.org/10.1016/S0140-6736(14)61228-9.

[91] M. Bourlière, S.C. Gordon, S.L. Flamm, C.L. Cooper, A. Ramji, M. Tong, N. Ravendhran, J.M. Vierling, T.T. Tran, S. Pianko, M.B. Bansal, V. de Lédinghen, R.H. Hyland, L.M. Stamm, H. Dvory-Sobol, E. Svarovskaia, J. Zhang, K.C. Huang, G.M. Subramanian, D.M. Brainard, J.G. McHutchison, E.C. Verna, P. Buggisch, C.S. Landis, Z.H. Younes, M.P. Curry, S.I. Strasser, E.R. Schiff, K.R. Reddy, M.P. Manns, K. V. Kowdley, S. Zeuzem, Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection, New England Journal of Medicine. 376 (2017) 2134–2146. https://doi.org/10.1056/NEJMoa1613512.

[92] C. Sarrazin, C.L. Cooper, M.P. Manns, K.R. Reddy, K. V. Kowdley, S.K. Roberts, H. Dvory-Sobol, E. Svarovskia, R. Martin, G. Camus, B.P. Doehle, L.M. Stamm, R.H. Hyland, D.M. Brainard, H. Mo, S.C. Gordon, M. Bourliere, S. Zeuzem, S.L. Flamm, No impact of resistance-associated substitutions on the efficacy of sofosbuvir, velpatasvir, and voxilaprevir for 12 weeks in HCV DAA-experienced patients, Journal of Hepatology. 69 (2018) 1221–1230. https://doi.org/10.1016/j.jhep.2018.07.023.

[93] P.S. Belperio, T.A. Shahoumian, T.P. Loomis, L.I. Backus, Real-world effectiveness of sofosbuvir/velpatasvir/voxilaprevir in 573 direct-acting antiviral experienced hepatitis C patients, Journal of Viral Hepatitis. 26 (2019) 980–990. https://doi.org/10.1111/jvh.13115.

[94] E.M. Said, B.A. Abdulaziz, M. El Kassas, I.H. El Attar, M. Emadeldeen, S.M. Abd-Elsalam, High success rates for the use of sofosbuvir/ombitasvir/paritaprevir/ritonavir + ribavirin and sofosbuvir/simeprevir/daclatasvir + ribavirin in retreatment of chronic hepatitis C infection after unsuccessful sofosbuvir/daclatasvir therapy: a real-life exp, Archives of Virology. 165 (2020) 1633–1639. https://doi.org/10.1007/s00705-020-04639-x.

[95] G.D. Huhn, M. Ramgopal, M.K. Jain, F. Hinestrosa, D.M. Asmuth, J. Slim, D. Goldstein, S. Applin, J.H. Ryu, S. Jiang, S. Cox, M. Das, T. Nguyen-Cleary, D. Piontkowsky, B. Guyer, L. Rossaro, R.H. Haubrich, HIV/HCV therapy with ledipasvir/sofosbuvir after randomized switch to emtricitabine-tenofovir alafenamide-based single-tablet regimens, PLOS ONE. 15 (2020) e0224875. https://doi.org/10.1371/journal.pone.0224875.

[96] M. Hussain, H. Galvin, T.Y. Haw, A. Nutsford, M. Husain, Drug resistance in influenza A virus: the epidemiology and management, Infection and Drug Resistance. Volume 10 (2017) 121–134. https://doi.org/10.2147/IDR.S105473.

[97] Influenza (Flu). Centers for Disease Control and Prevention website., www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm. Updated June 2, 2023. [Accessed August 3, 2023]., (2023).

[98] J.T. Nguyen, J.D. Hoopes, M.H. Le, D.F. Smee, A.K. Patick, D.J. Faix, P.J. Blair, M.D. de Jong, M.N. Prichard, G.T. Went, Triple Combination of Amantadine, Ribavirin, and Oseltamivir Is Highly Active and Synergistic against Drug Resistant Influenza Virus Strains In Vitro, PLoS ONE. 5 (2010) e9332. https://doi.org/10.1371/journal.pone.0009332.

[99] K. Melville, T. Rodriguez, H.M. Dobrovolny, Investigating Different Mechanisms of Action in Combination Therapy for Influenza, Frontiers in Pharmacology. 9 (2018). https://doi.org/10.3389/fphar.2018.01207.

[100] A.S. Perelson, L. Rong, F.G. Hayden, Combination Antiviral Therapy for Influenza: Predictions From Modeling of Human Infections, The Journal of Infectious Diseases. 205 (2012) 1642–1645. https://doi.org/10.1093/infdis/jis265.

[101] Y. Wang, G. Fan, A. Salam, P. Horby, F.G. Hayden, C. Chen, J. Pan, J. Zheng, B. Lu, L. Guo, C. Wang, B. Cao, Comparative Effectiveness of Combined Favipiravir and Oseltamivir Therapy Versus Oseltamivir Monotherapy in Critically Ill Patients With Influenza Virus Infection, The Journal of Infectious Diseases. 221 (2020) 1688–1698. https://doi.org/10.1093/infdis/jiz656.

[102] R.M. Mallory, S.O. Ali, T. Takas, M. Kankam, F. Dubovsky, L. Tseng, A phase 1 study to evaluate the safety and pharmacokinetics of MEDI8852, an anti-influenza A monoclonal antibody, in healthy adult volunteers, Biologicals. 50 (2017) 81–86. https://doi.org/10.1016/j.biologicals.2017.08.007.

[103] S.O. Ali, T. Takas, A. Nyborg, K. Shoemaker, N.L. Kallewaard, R. Chiong, F. Dubovsky, R.M. Mallory, Evaluation of MEDI8852, an Anti-Influenza A Monoclonal Antibody, in Treating Acute Uncomplicated Influenza, Antimicrobial Agents and Chemotherapy. 62 (2018). https://doi.org/10.1128/AAC.00694-18.

[104] E. Hershberger, S. Sloan, K. Narayan, C.A. Hay, P. Smith, F. Engler, R. Jeeninga, S. Smits, J. Trevejo, Z. Shriver, D. Oldach, Safety and efficacy of monoclonal antibody VIS410 in adults with uncomplicated influenza A infection: Results from a randomized, double-blind, phase-2, placebo-controlled study, EBioMedicine. 40 (2019) 574–582. https://doi.org/10.1016/j.ebiom.2018.12.051.

[105] S.E. Sloan, K.J. Szretter, B. Sundaresh, K.M. Narayan, P.F. Smith, D. Skurnik, S. Bedard, J.M. Trevejo, D. Oldach, Z. Shriver, Clinical and virological responses to a broad-spectrum human monoclonal antibody in an influenza virus challenge study, Antiviral Research. 184 (2020)

[106] ClinicalTrials.gov ID: NCT03040141., (Last Update Posted 2022-12-28).

[107] S. Z.A, C. Y, Z. W., Drug combinations. 1st ed.; In Comprehensive Pharmacology; Kenakin TP, Ed.; Elsevier: Oxford, UK, 2022. https://doi.org/NCT03040141.

[108] C.M. Heske, M.I. Davis, J.T. Baumgart, K. Wilson, M. V. Gormally, L. Chen, X. Zhang, M. Ceribelli, D.Y. Duveau, R. Guha, M. Ferrer, F.I. Arnaldez, J. Ji, H.-L. Tran, Y. Zhang, A. Mendoza, L.J. Helman, C.J. Thomas, Matrix Screen Identifies Synergistic Combination of PARP Inhibitors and Nicotinamide Phosphoribosyltransferase (NAMPT) Inhibitors in Ewing Sarcoma, Clinical Cancer Research. 23 (2017) 7301–7311. https://doi.org/10.1158/1078-0432.CCR-17-1121.

[109] W. Greco, H.D.. Unkelbach, G.. Pöch, J.. Sühnel, M.. & Kundi, W. Bödeker, Consensus on concepts and terminology for combined-action assessment: the Saariselkä agreement., Arch Complex Environ Stud. 4 (1992) 65–9.

[110] R.B. McFee, Middle East Respiratory Syndrome (MERS) Coronavirus, Disease-a-Month. 66 (2020) 101053. https://doi.org/10.1016/j.disamonth.2020.101053.

[111] M. Xu, E.M. Lee, Z. Wen, Y. Cheng, W.-K. Huang, X. Qian, J. TCW, J. Kouznetsova, S.C. Ogden, C. Hammack, F. Jacob, H.N. Nguyen, M. Itkin, C. Hanna, P. Shinn, C. Allen, S.G. Michael, A. Simeonov, W. Huang, K.M. Christian, A. Goate, K.J. Brennand, R. Huang, M. Xia, G. Ming, W. Zheng, H. Song, H. Tang, Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen, Nature Medicine. 22 (2016) 1101–1107. https://doi.org/10.1038/nm.4184.

[112] W. Sun, S. He, C. Martínez-Romero, J. Kouznetsova, G. Tawa, M. Xu, P. Shinn, E.G. Fisher, Y. Long, O. Motabar, S. Yang, P.E. Sanderson, P.R. Williamson, A. García-Sastre, X. Qiu, W. Zheng, Synergistic drug combination effectively blocks Ebola virus infection, Antiviral Research. 137 (2017) 165–172. https://doi.org/10.1016/j.antiviral.2016.11.017.

[113] M.M. Levine, Monoclonal Antibody Therapy for Ebola Virus Disease, New England Journal of Medicine. 381 (2019) 2365–2366. https://doi.org/10.1056/NEJMe1915350.

[114] L.A. Jackson, E.J. Anderson, N.G. Rouphael, P.C. Roberts, M. Makhene, R.N. Coler, M.P. McCullough, J.D. Chappell, M.R. Denison, L.J. Stevens, A.J. Pruijssers, A. McDermott, B. Flach, N.A. Doria-Rose, K.S. Corbett, K.M. Morabito, S. O'Dell, S.D. Schmidt, P.A. Swanson, M. Padilla, J.R. Mascola, K.M. Neuzil, H. Bennett, W. Sun, E. Peters, M. Makowski, J. Albert, K. Cross, W. Buchanan, R. Pikaart-Tautges, J.E. Ledgerwood, B.S. Graham, J.H. Beigel, An mRNA Vaccine against SARS-CoV-2 — Preliminary Report, New England Journal of Medicine. 383 (2020) 1920–1931. https://doi.org/10.1056/NEJMoa2022483.

[115] E.J. Anderson, N.G. Rouphael, A.T. Widge, L.A. Jackson, P.C. Roberts, M. Makhene, J.D. Chappell, M.R. Denison, L.J. Stevens, A.J. Pruijssers, A.B. McDermott, B. Flach, B.C. Lin, N.A. Doria-Rose, S. O'Dell, S.D. Schmidt, K.S. Corbett, P.A. Swanson, M. Padilla, K.M. Neuzil, H. Bennett, B. Leav, M. Makowski, J. Albert, K. Cross, V.V. Edara, K. Floyd, M.S. Suthar, D.R. Martinez, R. Baric, W. Buchanan, C.J. Luke, V.K. Phadke, C.A. Rostad, J.E. Ledgerwood, B.S. Graham, J.H. Beigel, Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults, New England Journal of Medicine. 383 (2020) 2427–2438. https://doi.org/10.1056/NEJMoa2028436.

[116] F.P. Polack, S.J. Thomas, N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, J.L. Perez, G. Pérez Marc, E.D. Moreira, C. Zerbini, R. Bailey, K.A. Swanson, S. Roychoudhury, K. Koury, P. Li, W. V. Kalina, D. Cooper, R.W. Frenck, L.L. Hammitt, Ö. Türeci, H. Nell, A. Schaefer, S. Ünal, D.B. Tresnan, S. Mather, P.R. Dormitzer, U. Şahin, K.U. Jansen, W.C. Gruber, Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine, New England Journal of Medicine. 383 (2020) 2603–2615. https://doi.org/10.1056/NEJMoa2034577.

[117] Emerging SARS-CoV-2 Variants. Centers for Disease Control and Prevention Website., https://www.cdc.gov/coronavirus/2019-ncov/more/science-and-research/scientific-brief-emerging–variants.html. Updated January 28, 2021. [Accessed May 14, 2021], (2021).

[118] Health Canada Product Monograph: Paxlovid (nirmatrelvir and ritonavir) co-packaged for oral use. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://covid-vaccine.canada.ca/info/pdf/paxlovid-pm-en.pdf [Accessed June 14, 2023] (2023).

[119] FDA News Release: FDA Approves First Oral Antiviral for Treatment of COVID-19 in Adults., https://www.fda.gov/news-events/press-announcements/fda-approves-first-oral-antiviral-treatment-covid-19-adults [Accessed June 14, 2023]., (2023).

[120] S. Chamakuri, S. Lu, M.N. Ucisik, K.M. Bohren, Y.-C. Chen, H.-C. Du, J.C. Faver, R. Jimmidi, F. Li, J.-Y. Li, P. Nyshadham, S.S. Palmer, J. Pollet, X. Qin, S.E. Ronca, B. Sankaran, K.L. Sharma, Z. Tan, L. Versteeg, Z. Yu, M.M. Matzuk, T. Palzkill, D.W. Young, DNA-encoded chemistry technology yields expedient access to SARS-CoV-2 M pro inhibitors, Proceedings of the National Academy of Sciences. 118 (2021). https://doi.org/10.1073/pnas.2111172118.

[121] J.A. Doudna, The promise and challenge of therapeutic genome editing, Nature. 578 (2020)

229–236. https://doi.org/10.1038/s41586-020-1978-5.

[122] M. Sun, S. Liu, X. Wei, S. Wan, M. Huang, T. Song, Y. Lu, X. Weng, Z. Lin, H. Chen, Y. Song, C. Yang, Aptamer Blocking Strategy Inhibits SARS-CoV-2 Virus Infection, Angewandte Chemie International Edition. 60 (2021) 10266–10272. https://doi.org/10.1002/anie.202100225.

[123] C. Tauber, R. Wamser, C. Arkona, M. Tügend, U. Bin Abdul Aziz, S. Pach, R. Schulz, D. Jochmans, G. Wolber, J. Neyts, J. Rademann, Chemical Evolution of Antivirals Against Enterovirus D68 through Protein-Templated Knoevenagel Reactions, Angewandte Chemie International Edition. 60 (2021) 13294–13301. https://doi.org/10.1002/anie.202102074.

[124] H.M. Ekiert, A. Szopa, Biological Activities of Natural Products, Molecules. 25 (2020) 5769. https://doi.org/10.3390/molecules25235769.

[125] S. Xu, L. Sun, B. Huang, X. Liu, P. Zhan, Medicinal chemistry strategies of targeting HIV-1 capsid protein for antiviral treatment, Future Medicinal Chemistry. 12 (2020) 1281–1284. https://doi.org/10.4155/fmc-2020-0084.

[126] R. Kasprzyk, T.J. Spiewla, M. Smietanski, S. Golojuch, L. Vangeel, S. De Jonghe, D. Jochmans, J. Neyts, J. Kowalska, J. Jemielity, Identification and evaluation of potential SARS-CoV-2 antiviral agents targeting mRNA cap guanine N7-Methyltransferase, Antiviral Research. 193 (2021) 105142. https://doi.org/10.1016/j.antiviral.2021.105142.

[127] J.L. Nieva, V. Madan, L. Carrasco, Viroporins: structure and biological functions, Nature Reviews Microbiology. 10 (2012) 563–574. https://doi.org/10.1038/nrmicro2820.

[128] K.M. White, R. Rosales, S. Yildiz, T. Kehrer, L. Miorin, E. Moreno, S. Jangra, M.B. Uccellini, R. Rathnasinghe, L. Coughlan, C. Martinez-Romero, J. Batra, A. Rojc, M. Bouhaddou, J.M. Fabius, K. Obernier, M. Dejosez, M.J. Guillén, A. Losada, P. Avilés, M. Schotsaert, T. Zwaka, M. Vignuzzi, K.M. Shokat, N.J. Krogan, A. García-Sastre, Plitidepsin has potent preclinical efficacy against SARS-CoV-2 by targeting the host protein eEF1A, Science. 371 (2021) 926–931. https://doi.org/10.1126/science.abf4058.

[129] K. Chayama, C. Hayes, HCV Drug Resistance Challenges in Japan: The Role of Pre-Existing Variants and Emerging Resistant Strains in Direct Acting Antiviral Therapy, Viruses. 7 (2015) 5328–5342. https://doi.org/10.3390/v7102876.

[130] N. Kurt Yilmaz, C.A. Schiffer, Introduction: Drug Resistance, Chemical Reviews. 121 (2021) 3235–3237. https://doi.org/10.1021/acs.chemrev.1c00118.